Supporting Information for:

Hyperbranched Polydisulfide

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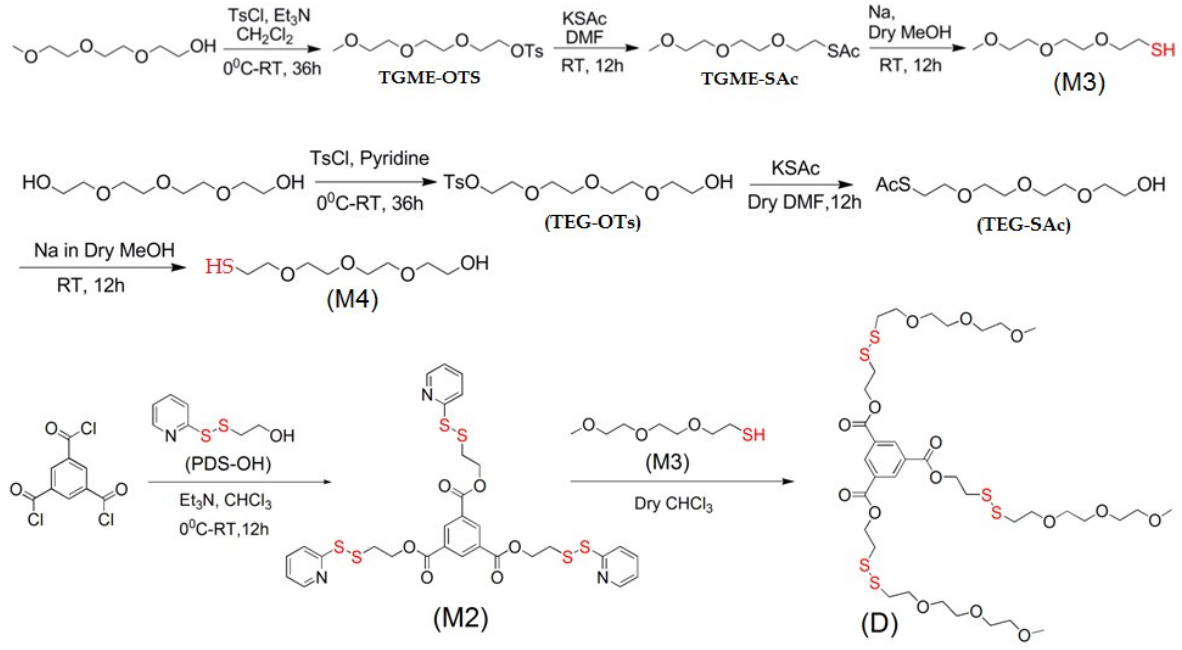
Materials and methods: Trimesoyl chloride, 2,2'-(ethane-1,2-diylbis(oxy)diethanethiol (**M1**), terephthaloyl chloride, poly(ethyleneglycol)thiol (PEG-SH), potassium thioacetate and other reagents were purchased from Sigma-Aldrich Chemical Co. and used without further purification. Solvents were purchased from commercially available sources and purified by standard methods. ^{1}H NMR spectra were recorded in Bruker DPX-300 MHz, DPX-400 MHz and DPX-500MHz NMR spectrometer and the spectra were calibrated against TMS as the internal standard. Spectroscopic grade solvents were used for UV/Vis studies and spectra were recorded in a Perkin Elmer Lambda 25 spectrometer. Mass spectrometric data were acquired by an electron spray ionization (ESI) technique on a Q-TOF-microquadruple mass spectrometer (Micro mass). TEM images were taken in JEOL-2010EX machine operating at an accelerating voltage of 200KV. Dynamic Light Scattering (DLS) measurements were carried out in Malvern instrument at a scattering angle of 173°. Fluorescence spectra were recorded in a FluoroMax-3 spectrophotometer, from Horiba Jobin Yvon. Molecular weight (M_n) and dispersity (Đ) of the polymers were measured by size exclusion chromatography (SEC) at 30 °C using a Waters GPC machine equipped with a 515 HPLC pump, Waters 2414 RI detector and HSPgel HT 4.0/HSPgel HT 2.5 columns connected in a series. THF was used as the eluent with a flow rate of 0.6 mL/ min. Molecular weight was estimated using a calibration plot generated from eight narrowly distributed polystyrene standards (PS) of known molecular weight and polydispersity index.

Synthesis: Synthesis of various small molecule thiols and model compounds is depicted in Scheme S1.



Scheme S1 Synthesis of various small molecule thiols (M3 and M4), monomer M2 and the dendritic model compound (D).

TGME-OTs: An aqueous solution of sodium hydroxide (1.5 g, 37.48 mmol in 20 mL) was added to a solution of triethylene glycol monomethyl ether (4.104g, 24.99mmol in 15 mL) and the mixture was stirred at 0 °C for 10 min. Subsequently a solution of p-toluene sulfonyl chloride in THF (5.24g, 27.49 mmol in 10 mL) was added dropwise to this cold solution and the mixture was stirred for further 4 h at 0 °C. After that the solution was extracted with ethyl acetate (3x30 mL) and the combined organic layer was washed with brine (2x20mL) and dried over anhydrous Na_2SO_4 to get the crude product as a colorless oil which was further purified by column chromatography (50 % ethyl acetate/hexane). Yield: (3.8 g, 68%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) : 7.79 (d, J = 8.5 Hz, 2H); 7.34 (d, J = 8.4 Hz, 2H); 4.16 (t, J = 5.0 Hz, 2H); 3.69-3.67 (m, 2H); 3.62-3.58 (m, 6H); 3.54-3.52 (m, 2H); 3.37 (s, 3H); 2.44 (s, 3H).

TGME-SAc: Potassium thioacetate (1.11g, 9.67mmol) was added to a solution of TGME-OTs (2.05g, 6.45 mmol) in dry DMF (10.0 mL) and the mixture was allowed to stir at rt for 12 h under argon atmosphere. Then the reaction was quenched by addition of 10.0 mL of water and extracted with ethyl acetate (3x20 mL). The combined organic solution was washed with brine (2x20 mL) and dried over anhydrous Na_2SO_4 to get crude product as a

brown oil which was further purified by column chromatography (50 % Ethyl acetate/ hexane) to get the desired product as a light yellow oil. Yield: (1.21g, 84%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm) : 3.66-3.53 (m, 10H); 3.38 (s, 3H); 3.09 (t, J = 6.6 Hz, 2H); 2.33 (s, 3H).

M3: Sodium (1.25g, 54.4mmol) was dissolved in dry methanol (6.0 mL) and then a solution of TGME-SAc in dry methanol (1.21g, 5.44mmol in 4 mL) was slowly added to it and the reaction mixture was allowed to stir at rt for 12h under argon atmosphere. After that the reaction was quenched by addition of 5.0 mL water and the solution was acidified with conc. acetic acid. The acidified solution was extracted with ethyl acetate (3x15 mL) and the combined organic solution was washed with brine wash (1x10mL) to get the crude product as a yellow oil which was further purified by column chromatography (50 % ethyl acetate/ hexane mixture) to get the desired product as a light yellow oil. Yield: (0.66g, 82%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ(ppm) : 3.67-3.53 (m, 10H); 3.38 (s, 3H); 2.73-2.66 (m, 2H); 1.58 (t, J = 8.1 Hz, 1H).

TEG-OTs: Pyridine (4.2 mL, 51.75mmol) was added to a solution of TEG-OH (2.01g, 10.35 mmol) in dry chloroform (25.0 mL). The mixture was cooled in an ice bath and then a solution of p-toluene sulfonyl chloride in DCM (2.17g, 11.38mmol in 10 mL) was added dropwise to it. The reaction mixture was allowed to stir at 0°C-rt for 24 h under argon atmosphere. After that the reaction mixture was washed with 0.1N HCl (2x10 mL), followed by saturated sodium bicarbonate solution (2x10 mL). The combined organic layer was washed with brine (2x20 mL) and dried over anhydrous Na_2SO_4 and solvent was evaporated to the get crude product which was further purified by column chromatography to get the desired product as a white solid. Yield: (1.72g, 48%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) : 7.79 (d, J = 8.4 Hz, 2H); 7.34 (d, J = 8.4 Hz, 2H); 4.23-4.11 (m, 2H); 3.74-3.59 (m, 15H); 2.44 (s, 3H).

TEG-SAc: Potassium thioacetate (0.688g, 6.03mmol) and TEG-OTs (1.4g, 4.02 mmol) were dissolved in dry DMF (8.0 mL) and the mixture was allowed to stir at rt for 12 h under argon atmosphere. Then the reaction was quenched by addition of 8.0 mL of water. The crude mixture was extracted with ethyl acetate (3x15mL) and the combined organic solution was washed with brine (2x10 mL), dried over Na_2SO_4 and the solvent was evaporated to get the crude product as a light brown oil. It was further purified by column chromatography (eluent- 50 % ethyl acetate/ hexane) to get the desired product as light orange color oil. Yield: (0.62g,

85%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ(ppm): 4.22 (t, J = 4.8 Hz, 2H); 3.73-3.57 (m, 13H); 3.08 (t, J = 6.6 Hz, 2H); 2.33 (s, 3H).

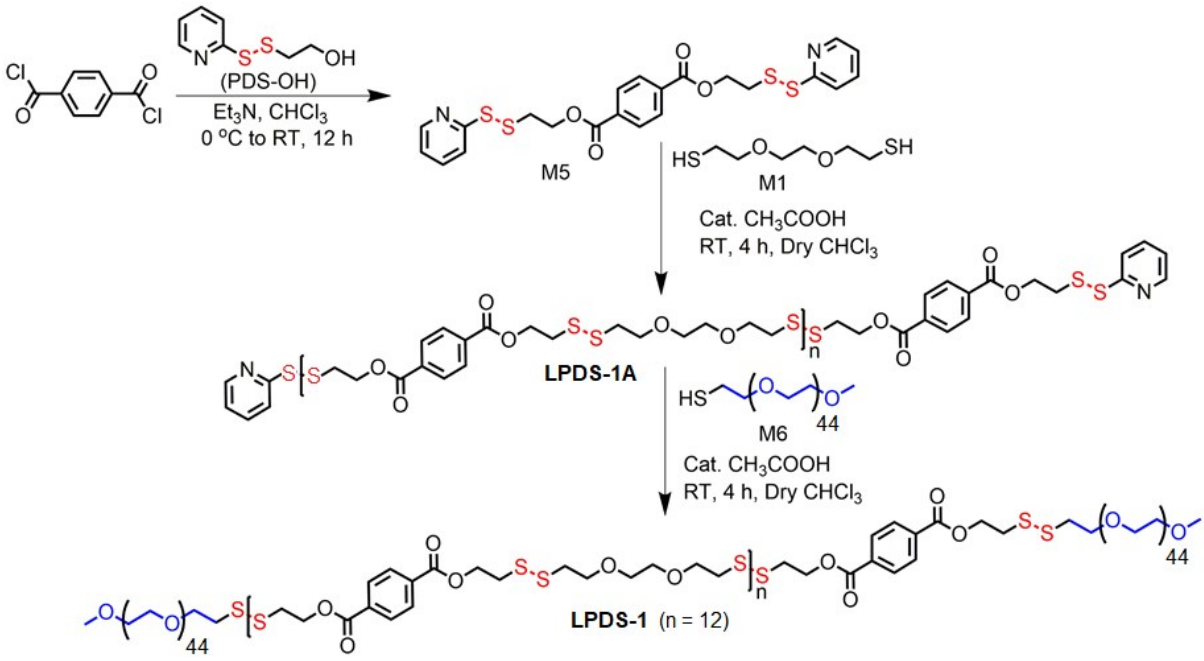
M4: Sodium (0.81g, 35.2mmol) was dissolved in dry methanol (5.0 mL) and then a solution of TEG-SAc in methanol (0.9g, 3.52mmol, 3 mL) was slowly added to it and the reaction mixture was allowed to stir at rt for overnight under argon atmosphere. After that the reaction was quenched by addition of 4.0 mL water. Methanol was evaporated under reduced pressure and the remaining solution was acidified with acetic acid. The acidified solution was extracted with ethyl acetate (3x10 mL) and the combined organic solution was washed with brine to get the crude product as a light brown oil which was further purified by column chromatography (ethyl acetate/ hexane mixture) to get the desired product as a yellow oil. Yield: (0.61g, 74%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ(ppm) : 3.75-3.60 (m, 15H); 2.71 (t, J = 7.5 Hz, 2 H); 1.62 (t, J = 7.5 Hz, 1H).

Monomer M2: 2-(pyridin-2-yldisulfanyl) ethanol (PDS-OH) (1.19 g, 6.36 mmol) and triethyl-amine (1.1 mL, 7.68 mmol) was dissolved in dry DCM (10.0 mL) in a round bottom flask and placed on an ice-water bath for 10 min. To this cold solution trimesoyl chloride (0.512g, 1.92 mmol) was added drop-wise and then the reaction mixture was stirred under argon atmosphere for 12h at rt. Stirring was stopped and the organic layer was washed with brine solution (3x10 mL) and dried over anhydrous Na_2SO_4 and solvent was evaporated to get the crude product as an off white semi-solid. It was then purified by column chromatography (ethyl acetate hexane = 3: 7) to get M2 as a colorless semi solid.

Yield (1.89g, 70%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) : 8.83 (s, 3H), 8.44 (d, J = 4.4 Hz, 3H), 7.69 (t, J = 8.0 Hz, 3H), 7.61 (t, J = 8.0 Hz, 3H), 7.08 (t, J = 5.2 Hz, 3H), 4.64 (t, J = 6.4 Hz, 6H), 3.22 (t, J = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ(ppm) : 164.1, 159.0, 149.3, 136.6, 134.4, 130.6, 120.5, 119.5, 62.9, 36.7; HRMS:$[M+Na]^+$ calculated [740.0124] and found [740.0123].

Dendritic model compound (D): M3 (0.063 g, 0.087 mmol) and M4 (0.054g, 0.304 mmol) were dissolved with dichloromethane (DCM) (1.0 mL) in a schlenk flask and to this solution two drops of CH_3CO_2H was added. The reaction mixture was stirred at rt for 12h under argon atmosphere. Then the solvent was evaporated and the crude product was purified by column chromatography (ethyl acetate: hexane = 7: 3) to get compound D as colorless semi-solid. Yield: (0.058g, 72%).^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 8.86 (s, 3H); 4.64 (t, J = 6.6 Hz, 6H); 3.75 (t, J = 6.6 Hz, 6H); 3.65-3.62 (m, 18H); 3.57-3.52 (m, 6H); 3.37 (s, 9H); 3.07 (t, J = 6.6 Hz, 6H); 2.93 (t, J = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ(ppm): 164.8, 135.0,

131.3, 72.1, 70.7, 70.6, 69.7, 63.8, 59.2, 38.8, 37.1, 29.8; HRMS: $[M+Na]^+$ calculated [947.2156] and found [947.1064].



Scheme S2 Synthesis of monomer M5 and control polymer LPDS-1.

Monomer M5: Monomer **M5** was synthesized following the similar procedure of monomer M2. 2-(pyridin-2-yldisulfanyl) ethanol (PDS-OH) (553 mg, 2.955 mmol) and triethyl-amine (0.49 mL, 3.54 mmol) were dissolved in dry DCM (5.0 mL) in a round bottom flask and stirred on an ice-water bath for 10 min. To this cold solution Terephthaloyl chloride (250 mg, 1.231 mmol) in 5 mL DCM was added drop-wise and then the reaction mixture was stirred under argon atmosphere for 12h at rt. The stirring of the reaction was stopped and organic layer was washed with brine solution (3x10 mL) and dried over anhydrous Na_2SO_4 and solvent was evaporated to get the crude product as white semi-solid. Product was then purified by column chromatography using ethyl acetate: hexane = 1: 3 as an eluent to obtain M5 as white colored solid.

Yield (350 mg, 56 %); ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) : 8.46 (d, J = 4.8 Hz, 2H), 8.08 (s, 2H), 7.69 (t, J = 8.0 Hz, 2H), 7.58 (t, J = 8.0 Hz, 2H), 7.08 (t, J = 6.2 Hz, 2H), 4.61 (t, J = 6.4 Hz, 4H), 3.22 (t, J = 6.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ(ppm) : 165.5, 159.64, 149.70, 137.41, 133.91, 129.83, 121.14, 120.24, 63.26, 37.59; HRMS: $[M+H]^+$ calculated [505.0384] and found [505.0385].

Synthesis of LPDS-1A: M1 (32.8 mg, 0.180 mmol) and M5 (100 mg, 0.198 mmol) were dissolved in dry degassed dichloromethane (DCM) (150 µL) in a glass schlenk flask with a magnetic stirrer and to this 1-2 drops of CH_3CO_2H was added. The reaction mixture was

stirred at 25°C for 4h under argon atmosphere. The viscous solution was then precipitated from excess of cold methanol. The light yellow precipitate was re-dissolved in DCM, and re-precipitated from cold methanol and dried under vacuum to obtain LPDS-1A as an off white sticky mass. Yield: (80.0 mg, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.44 (bs, 2H); 8.1 (s, 4H); 7.75 (m, 2H); 7.65-7.59 (t, J = 5.8 Hz, 2H); 7.15 (m, 2H); 4.624 (t, J = 6.6 Hz, 4H); 3.764-3.73 (t, J = 6.6, 4H); 3.627 (bs, 4H); 3.059 (t, J = 6.6, 4H); 2.922 (t, J = 6.6 Hz, 4H). M_w = 9000 g/mol (Đ = 1.52) from SEC in THF.

Synthesis of LPDS-1: LPDS-1A (40 mg, 0.00658 mmol) and compound M6 (27.63 mg, 0.0138 mmol) were dissolved in DCM (0.4 mL) in a glass schlenk flask and two drops of acetic acid was added to this solution. The reaction mixture was stirred at rt for 4h under argon atmosphere. The viscous solution was precipitated from excess of cold diethyl ether. The precipitate was re-dissolved in DCM, and re-precipitated from cold diethyl ether and dried under vacuum to obtain LPDS-1 as white solid. Yield: (55 mg, 82%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.1 (s, 4H); 4.62 (t, J = 6.5 Hz, 4H); 3.76-3.73 (m, 4H); 3.65-3.60 (m, 4H); 3.373 (s, 6H); 3.15-3.05 (t, J = 6.5 Hz, 4H).2.95-2.85 (t, J = 6.5 Hz, 4H).

Estimation of disulfide weight % in amphiphilic polymers: Combining the SEC (Fig. S1) determined molecular weight of **P1** and UV/Vis data (Fig. S2), average number of Py-Ds groups per polymer was estimated to be 22. Considering relative peak integration of H_a and H_d in the NMR spectrum (Fig. 1), the ratio of the phenyl / Py-Ds was estimated to be 1:1.08. Therefore on average, total number of phenyl units in **P1** = 22/1.08 = 20.37. Each phenyl ring contains three disulfide units and therefore on an average total number of disulfide groups in **P1** = 61.11 which should be same for **P2**. So total molecular weight of disulfide in **P2** = 64.12 x 61.11 = 3918.3. Considering M_w of **P2** = 17000, weight % of disulfide in **P2** = (3918.3/17000) x100 % = 23.1%. Similarly for the linear polymers, considering repeating unit structure, degree of polymerization of the polydisulfide block and overall molecular weight of the polymer, disulfide weight % could be estimated to be approximately 8.9 % and 16 %, respectively, for **LPDS** and **LPDS-1**.

Additional Figures:

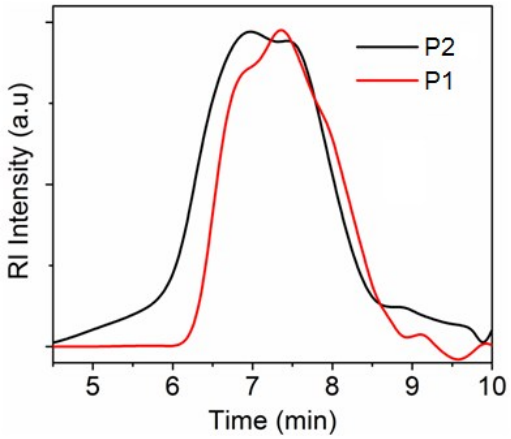


Fig. S1 SEC traces of P1 and P2 in THF.

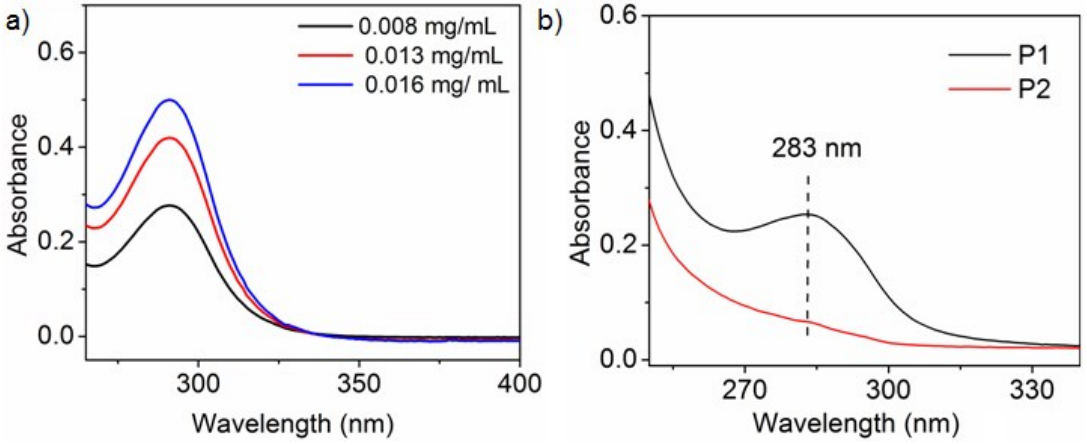


Fig. S2 a) Concentration dependent UV/Vis spectra of PDS-OH in $CHCl_3$; b) UV/Vis spectra of polymer P1 (c = 0.026 mg/mL) and P2 (0.03 mg/mL) in $CHCl_3$ (path length = 1.0 cm).

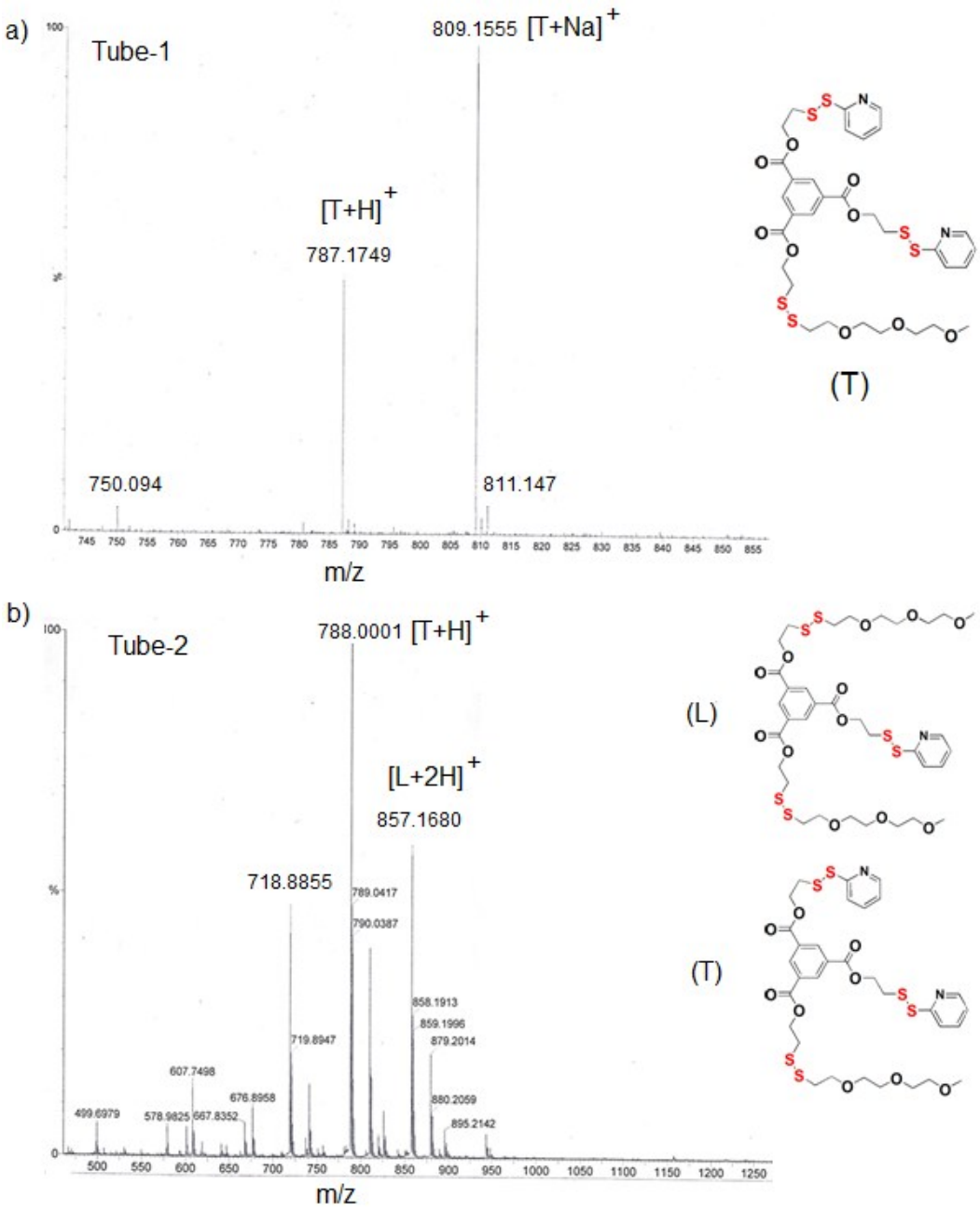


Fig. S3 HRMS (ESI) of the crude reaction mixture of a) Tube-1 and b) Tube-2 along with assignments of specific peaks along with the structure of linear (L) or terminal (T) model compounds. For description on the contents of tube-1 and tube-2, please see the discussion and Figure 2 in the main text.

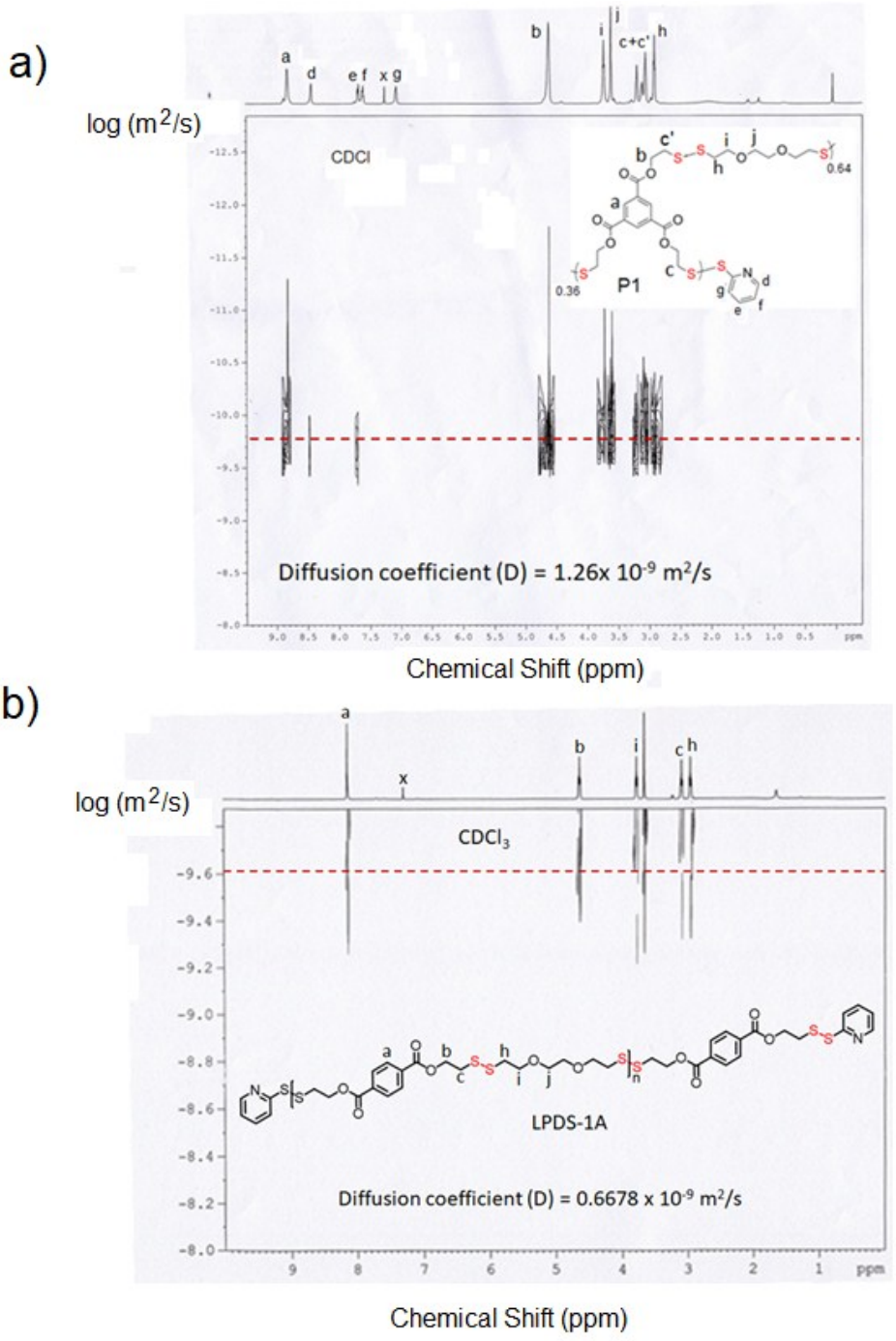


Fig. S4 DOSY spectra of a) P1 and b) LPDS-1A in $CDCl_3$ at 25 ˚C (X indicates peak from residual solvent).

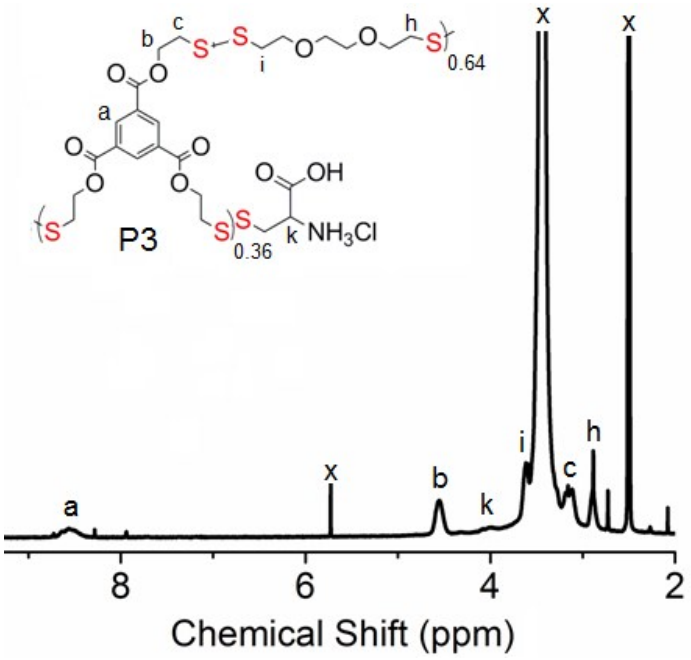


Fig. S5 ^{1}H NMR of P3 in DMSO-d_6 (x indicates peaks from residual solvent).

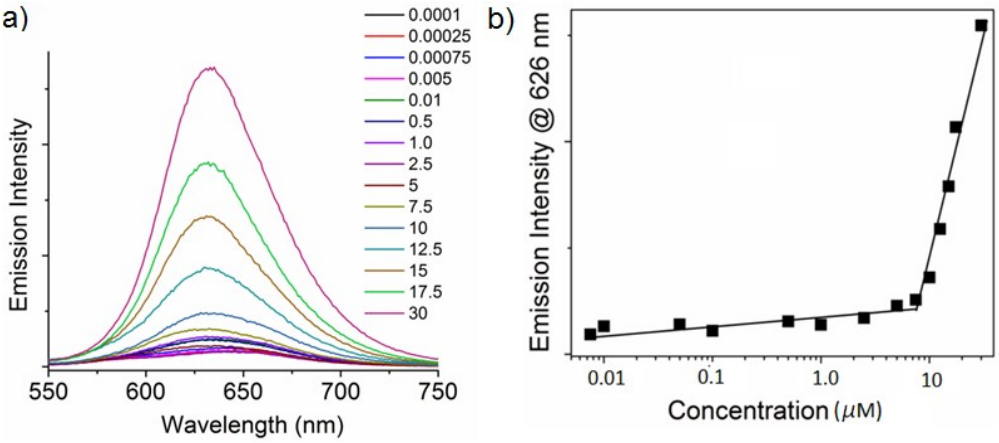


Fig. S6 a) Emission spectra of Nile Red (encapsulated in aqueous solution of P2) at varying concentrations of the polymer (numbers inside the figures indicate the polymer concentration in *μM)*; b) Plot of emission intensity (λ_{em} = 626nm) as a function of concentration of P2. (Nile Red concentration was kept constant at 10.0 μM).

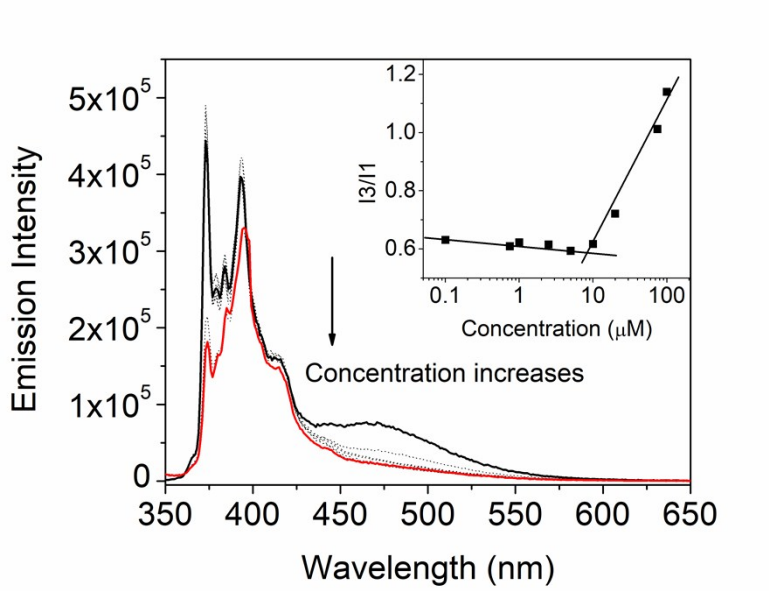


Fig. S7 Emission spectra of pyrene (encapsulated in aqueous solution of P2) at varying concentrations of the polymer; Inset- Variation of emission intensity (λ_{ex} = 337 nm) as a function of concentration of P2. (Pyrene concentration was kept constant at 10.0 μM).

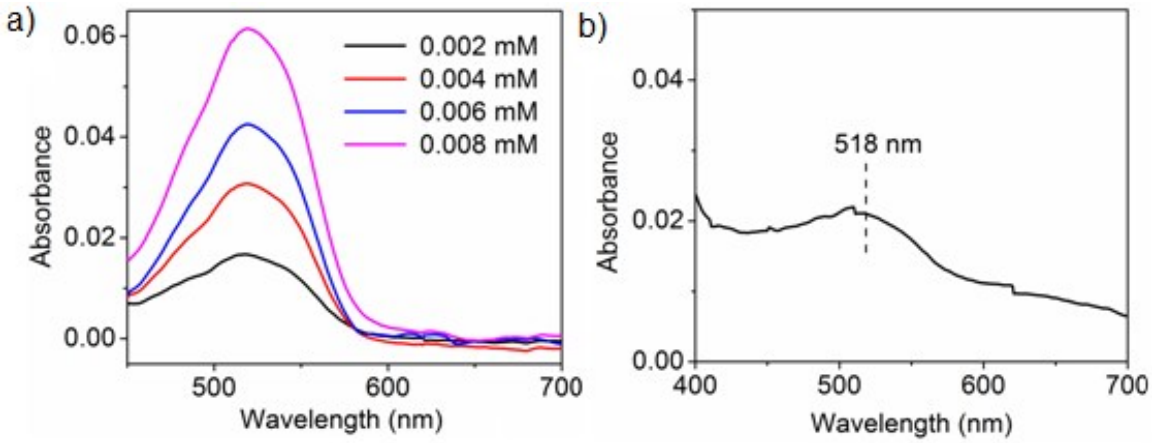


Fig. S8 a) Concentration dependent UV/Vis spectra of Nile Red in $CHCl_3$; b) UV/ Vis spectra of NR encapsulated P2 (C = 10.0 μM) after freeze-drying and re-dissolving in $CHCl_3$ (path length = 1.0 cm).

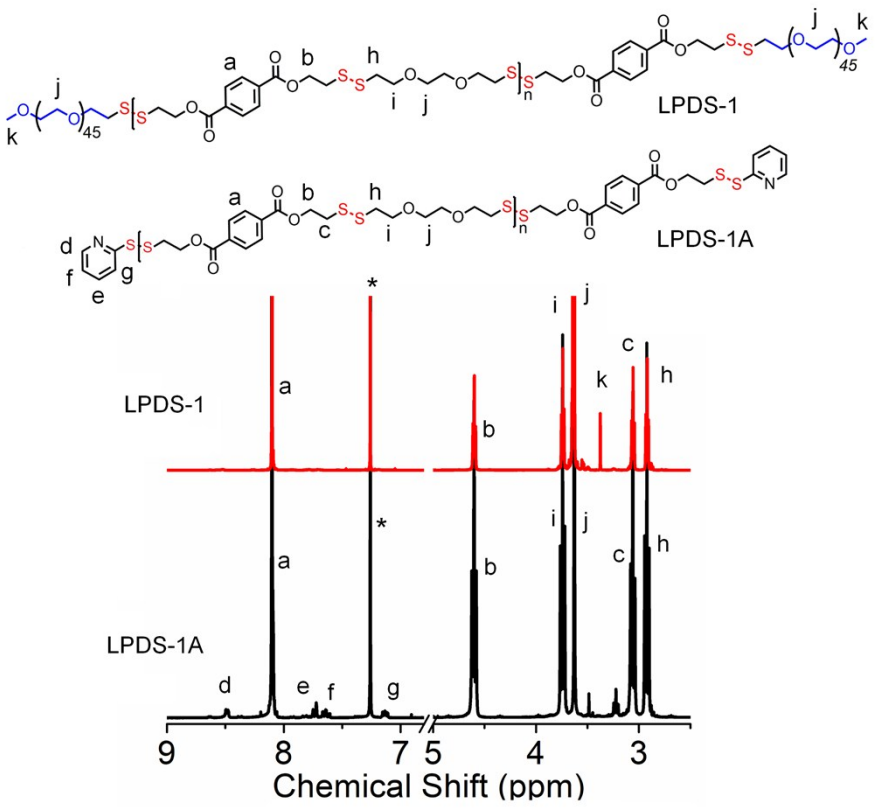


Fig. S9 ^{1}H NMR spectra of LPDS-1A and LPDS-1 in $CDCl_3$ (* indicates residual solvent from $CDCl_3$).

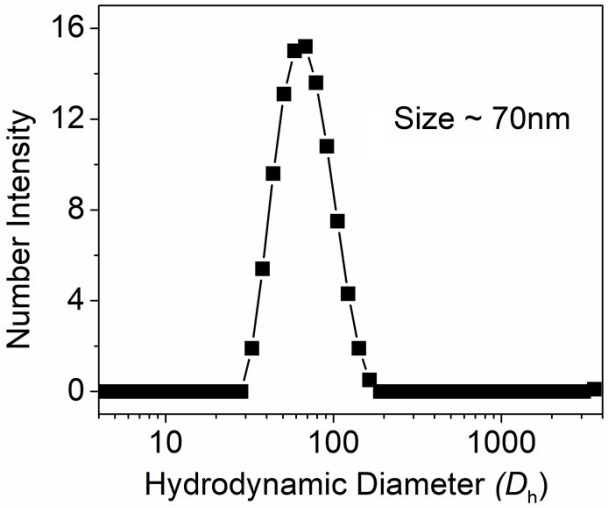


Fig. S10 DLS profile of aqueous aggregates of LPDS-1 (C = 100.0 μM).

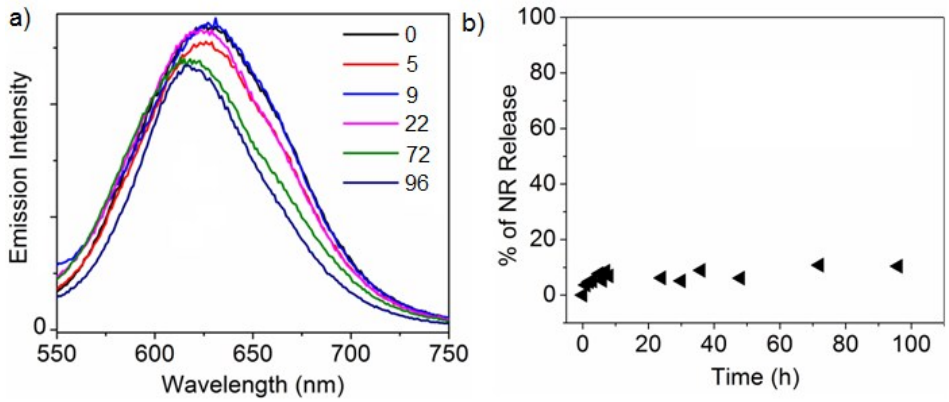


Fig. S11 Time dependent (number inside the figure indicate time in hour) emission spectra (λ_{ex} = 530 nm) of Nile Red encapsulated P2 (C = 50 μM) in the absence of GSH; b) % of Nile Red release as a function of time.

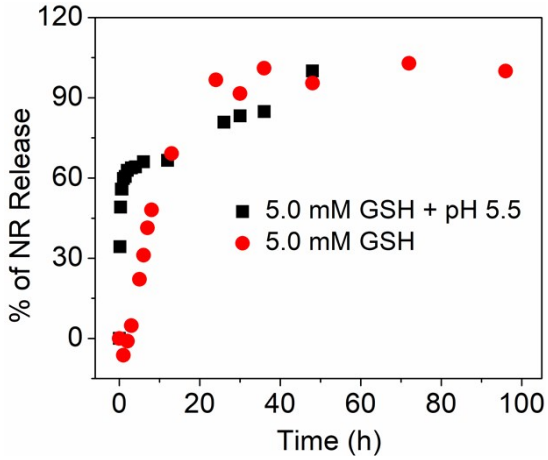


Fig. S12 % of Nile Red release as a function of time (in h) upon treatment with 5.0 mM GSH in neutral (red circle) and acidic (pH ~ 5.5) (black square) aqueous solutions.

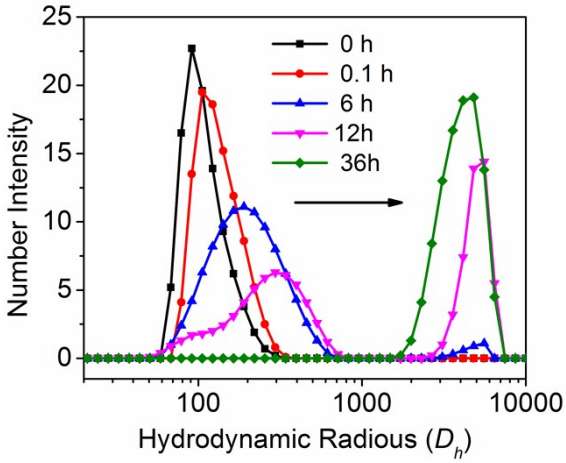


Fig. S13 Time dependent DLS profile of aqueous solution P2 (C = 100 μM) after addition of 20.0 mM GSH. Numbers inside the figure indicates time in hour.

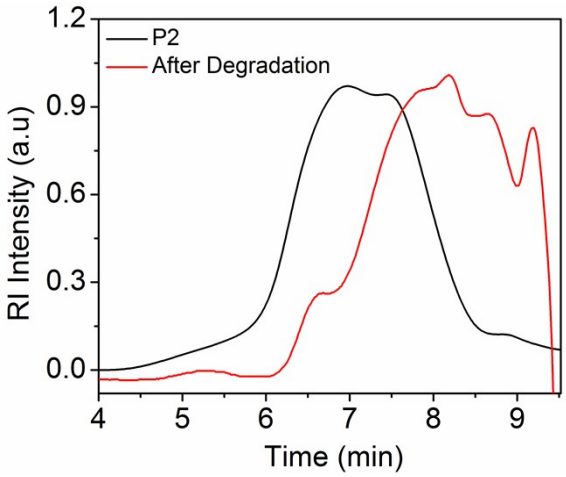


Fig. S14 SEC traces of P2 in THF before (black) and after (red) treating it with 20.0 mM GSH for 72h.

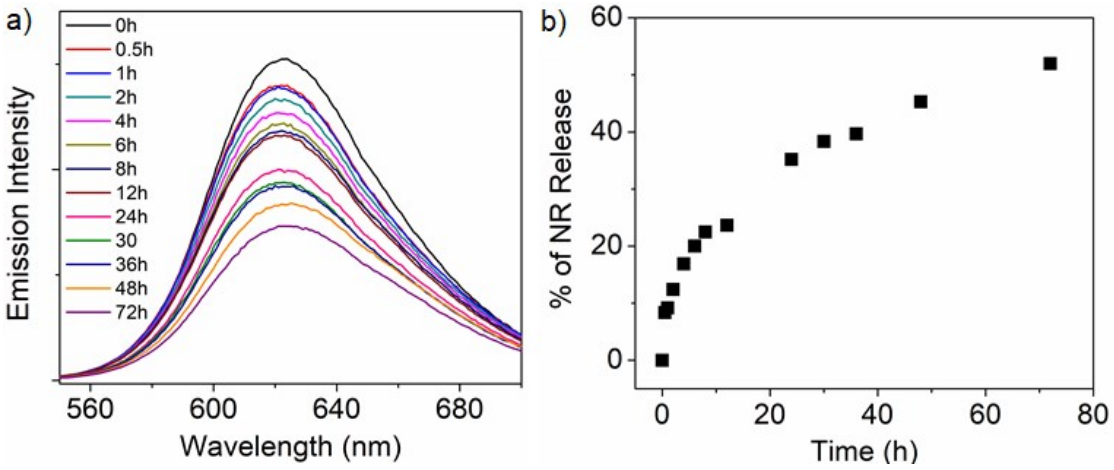


Fig. S15 Time dependent (numbers inside the figure represent time in h) emission spectra (λ_{ex} = 530 nm) of NR-encapsulated in LPDS-1 in presence of 5.0 mM GSH; b) % of NR release as a function of time upon treatment with 5.0 mM GSH.